REMARKS

Claims 17, 21-23, 25, 27 and 29-32 have been withdrawn from further consideration as being drawn to non-elected subject matter, and claims 18-20, 24, 26, 28 and 32 have been rejected under 35 U.S.C. § 112, first paragraph, and under 35 U.S.C. § 103. Applicants respectfully request reconsideration and withdrawal of these rejections for the reasons stated below.

REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, WRITTEN DESCRIPTION

Claims 18-20, 24, 26, 28 and 32 have been rejected under 35 U.S.C. § 112, first paragraph, as not being adequately described in the specification. During the December 2, 2009 interview with Examiners Jean-Louis and Padmanbhan, Applicants' representative and the Examiners discussed the written support for "reducing a risk of developing". Specifically, Applicants' representative directed the Examiners to page 3, lines 8-15 of the specification, which states "The present method may be applied to human skin which is already dry ... or to healthy skin to prevent or ***reduce*** such deteriorative changes" (emphasis added).

While "reducing the risk of" encompasses "preventing", the issue under this rejection is whether one would reasonably understand from the specification that the inventors had possession of "reducing the risk of developing vaginal dryness". Thus, Applicants should not be held to a standard that the specification must provide data establishing prevention, so long as one would have reasonably understood that reducing the risk of vaginal dryness is disclosed. The Examiner stated that they would reconsider this rejection in view of this portion of the specification. Thus, Applicants respectfully request that this rejection be reconsidered and withdrawn.

REJECTION UNDER 35 U.S.C. § 103

Claims 18, 19, 24, 26, 28 and 32 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Kragie[1] in view of Willhite[2]. Claim 20 has been rejected under 35 U.S.C. § 103(a) as being unpatentable over Kragie in view of Willhite and Younglai[3]. Claims 18, 19, 24, 26, 28 and 32 have also been rejected under 35 U.S.C. § 103(a) as being unpatentable over the Sitruk-Ware[4] in view of Spicer[5] and Willhite. Claim 20 has also been rejected under 35 U.S.C. § 103(a) as unpatentable over Sitruk-Ware in view of Spicer, Willhite and Younglai. Applicants respectfully traverse these rejections because there was no reasonable expectation in the art that the recited estrogenic component would be pharmacologically useful, and because it was unexpected to discover that the recited estrogenic component is pharmacologically useful.

Claim 28 has been amended to recite the limitation previously contained in claim 20. Claim 20 has, therefore, been cancelled. Thus, for the purposes of this response, it is assumed that the rejection of claim 20 now applies to claim 28, and each claim depending directly or indirectly from claim 28.

I. THE CLAIMED INVENTION

The invention as recited in claim 28, as amended, is directed to a method of treating or preventing vaginal dryness comprising applying a composition. The composition contains at least 5 μg/g of an estrogenic component. The estrogenic component is selected from the group consisting of substances represented by the following formula:

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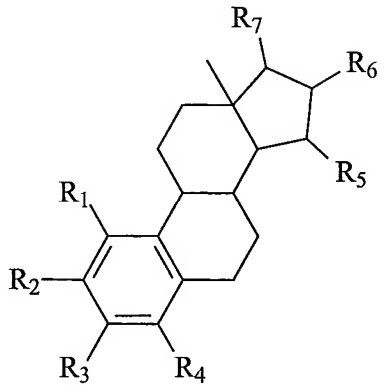
[1] United States Published Patent Application Number 2004/0192598 to Kragie ("Kragie").

[2] Willhite *et al.*, "Urogenital Atrophy: Prevention and Treatment," PHARMACOTHERAPY (2001) 21(4): 464-480 ("Willhite").

[3] Sitruk-Ware *et al.*, "Local hormonal treatment for urogenital atrophy after menopause," Schweiz. Rundsch., Med. Praxis (1997) 86(33): 1245-1248 ("Sitruk-Ware").

[4] Sitruk-Ware *et al.*, "Local hormonal treatment for urogenital atrophy after menopause," Schweiz. Rundsch., Med. Praxis (1997) 86(33): 1245-1248 ("Sitruk-Ware").

[5] United States Patent Number 5,21,952 to Spicer ("Spicer").



in which formula R_1, R_2, R_3, R_4, independently are a hydrogen atom, a hydroxyl group or an alkoxy group with 1-5 carbon atoms; each of R_5, R_6, R_7 is a hydroxyl group; no more than 3 of R_1, R_2, R_3, R_4 are hydrogen atoms; precursors capable of liberating a substance according to the aforementioned formula when used in the present method, wherein the precursors are derivatives of the estrogenic substances wherein the hydrogen atom of at least one of the hydroxyl groups has been substituted by an acyl radical of a hydrocarbon carboxylic, sulfonic acid or sulfamic acid of 1-25 carbon atoms; tetrahydrofuranyl; tetrahydropyranal; or a straight or branched chain glycosydic residue containing 1-20 glycosidic units per residue; and mixtures thereof. In one embodiment, the estrogenic component is estetrol. The composition also contains a cosmetically acceptable vehicle. Claims 18, 19, 24, 26 and 32-34 depend from claim 28.

II. THE CITED REFERENCES

The Patent Office contends that Kragie teaches using estrogen function replacement agent(s) to treat vaginal atropy, and that Willhite teaches that vaginal atropy is synonymous with vaginal dryness.[6] Kragie is directed to compositions and methods to replace estrogen in humans and other animals.[7] It describes a method for alleviating adverse side effects and/or enhancing the beneficial efficacy of an aromatase inhibitor in a subject by administering a combination of an aromatase inhibitor and an estrogen function replacement (EFR) agent. An EFR agent "is defined as one that can selectively, totally, or partially

[6] Office Action at pages 9-10.

[7] Kragie at abstract.

replace the function performed by the estrogen compounds that are usually synthesized by the aromatase enzyme."[8] Kragie provides an overly broad list of EFR agents, which include: estradiol, ethinyl estradiol, estradiol valerate, estradiocypionate, estrone, estriol, estetrol, estropipate, 2-methoxyestradiol, hydroxyestrones, sodium estrone sulfate, equine estrogens, equilenin, equilin, conjugated estrogens, esterified estrogens, micronized estrogens, synthetic estrogens, nonsteroidal estrogens; phytoestrogens such as isoflavonoids, flavonoids, lignans, coumestan, and other natural compounds derived from plants such as soya, tea, fruits and vegetables; synthetic phytoestrogen ipriflavone; genistein, daidzein, enterolactone; selective estrogen receptors ligands and modulators factors (such as raloxifene, tamoxifen, indenoindoles, and estrogen partial agonist/antagonists); catechol estrogens and their metabolites (such as 2-hydroxyestrone, 2-hydroxyestradiol and their 4-hydroxy isomers); 2,3-estrogen o-quinone, diethylstilbestrol, nitro-estrogens, catechol estrogen 3,4-quinone, estrophilin, formatrix, methallenestril, quinestrol, chlorotrianisene, norethisterone, norethindrone, 17-alpha-ethynyl-19-nortestosterone; dienestrol, norethynodrel, promethestrol, mestranol, tamoxifen, hydroxytamoxifen, clomiphene, chlorotrianisene, nafoxidine, hexestrol, niifepristone, RU 486; bisphenol A, p-tert-octylphenol and other endocrine disruptors; B-ring homologated estradiol analogues; estrogen receptor elements (such as estrogen receptor activation factor, activated estrogen receptor complex, and Heat Shock Protein).[9] However, at the relevant time, one of ordinary skill in the art would not have picked estetrol from this long list, or even considered using estetrol when the relevant scientific literature taught that estetrol was believed not to be pharmacologically useful.

Kragie notes that EFR agents are currently used in perimenopausal and menopausal women.[10] Spefically, Kragie states that "... EFR agents are currently used in perimenopausal and menopausal women to prevent and/or treat vaginal atrophy, hypogonadism, diminished libido and to relieve vasomotor symptoms, urogenital atrophy, osteoporosis, alopecia and other symptoms and signs associated with menopause."[11]

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[8] Kragie at ¶ 13.

[9] Kragie at ¶¶ 38 and 39.

[10] Kragie at ¶ 73.

[11] Kragie at ¶ 73.

The Office Action cites Willhite as demonstrating "[t]hat urogenital atrophy is also known as vaginal dryness."[12]

The Office Action cites Younglai as teaching "estetrol (i.e. E4) has many precursors (see pg. 1617, figure 2). In fact, Younglai et al. teach 15-α-hydroxyandrostenedione or dehydroxyandrostenedione as precursors of E4 and containing acyl moiety group (instant claim 20)."[13]

The Patent Office also contends that the combination of Sitruk-Ware, Willhite and Younglai likewise suggest the recited invention.[14] The Patent Office contends that Sitruk-Ware teaches that estrogenic treatment is an efficient way to correct vaginal dryness.[15] Sitruk-Ware specifically teaches that "[t]he post-menopausal urogenital symptoms connected with low estrogen level are manifested after several years of hormonal deficit and are generally frequent in untreated elderly women. Estrogenic therapeutics, which are administered systemically or genitally, for the most part are capable of rapidly correcting or at least ameliorating the symptoms."[16] It further states that "[p]ost-menopausal low estrogen level will, in the medium term, be manifested at the urogenital level by irritation and vaginal dryness, ..."[17] Although it states that "[a]ny systemic estrogenic therapeutic is, of course, understood as being capable of correcting urogenital symptoms, ..."[18], Sitruk-Ware only discusses the following estrogens: estriol, promestriene, estradiol, estrone – conjugated estrones.[19] The Patent Office acknowledges that Sitruk-Ware does not address the use of estetrol.[20]

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[12] Office Action at page 14.

[13] Office Action at page 12.

[14] Office Action at pages 13-16.

[15] Office Action at page 13.

[16] Sitruk-Ware at page 2, lines 2-7.

[17] Sitruk-Ware at page 3, lines 15-18.

[18] Sitruk-Ware at page 4, lines 7-9.

[19] Sitruk-Ware at pages 4-10.

[20] Office Action at page 14.

To address this short-coming, the Patent Office contends that Spicer teaches that estetrol may be employed in compositions formulated for vaginal delivery.[21] Spicer describes a method for inhibiting conception in mammals, especially human females, and to formulations for use in such methods.[22] Specifically, Spicer states that:

> in accordance with the present invention there is provided a contraceptive delivery system and method for preventing pregnancy in a mammal (in particular, a human female) which comprises administering over an extended period of time (on the order of about 2 to about 6 months) an amount of a GnRH composition effective to suppress LH and FSH (with resultant inhibition of ovulation and ovarian sex-steroid production); an amount of an estrogenic steroid effective to counteract the possibility of side effects which may develop during prolonged therapy with GnRH, including but not limited to: symptoms of the menopause, vasomotor instability, loss of bone mineral content, rise in serum total or low-density cholesterol or its fractions, and urogenital atrophy; together with a short-term administration (on the order of about 5 to 20 days, preferably 10 to 15 days) of an amount of progestational steroid effective to counteract the possibility of endometrial hyperstimulation, hyperplasia or carcinoma which may develop during prolonged therapy with estrogenic steroids.[23]

Like Kragie, Spicer also provides an overly broad list of estrogens. Specifically, Spicer states that

> [n]atural and synthetic estrogenic compositions which can be used according to the invention described herein include natural estrogenic hormones and congeners, including but not limited to estradiol, estradiol benzoate, estradiol cypionate, estradiol valerate, estrone, diethylstilbestrol, piperazine estrone sulfate, ethinyl estradiol, mestranol, polyestradiol phosphate, estriol, estriol hemisuccinate, quinestrol, estropipate, pinestrol and estrone potassium sulfate. Equine estrogens, such as equilelinin, equilelinin sulfate and estetrol, may also be employed.[24]

However, there is no reason why one would pick estetrol from this long list where estetrol is listed as a mere possibility rather than part of the invention, or would consider using estetrol when the relevant scientific literature taught that estetrol was believed not to be pharmacologically useful.

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[21] Office Action at page 14.

[22] Spicer at column 1, lines 6-8.

[23] Spicer at column 3, lines 32-52.

[24] Spicer at column 5, lines 50-61.

III. ARGUMENT

In the Office Action of August 18, 2009, the Examiner contends "that it would have been well within the purview of the skilled artisan to utilize and to try estetrol since Kragie teaches the use of estetrol as an EFR agent in the treatment of vaginal atrophy and urogenital atrophy and given the teaching of Kragie that weak EFR agent can be used at the appropriate dosage in order to provide sufficient biological activity for the desired estrogen function at the target site."[25] However, as discussed during the interview of December 2, 2009, one of ordinary skill in the art would not have reasonably believed that estetrol could have been used in a method of treating or reducing a risk of developing vaginal dryness because no one appreciated estetrol's long elimination half life, and instead believed that it had a short elimination half life and low receptor affinity.

Point I. Estetrol differs from other estrogens, and can be considered a SERM; therefore, one would not have reasonably expected Estetrol to be pharmacologically useful.

On December 2, 2009, Applicants' representative discussed the history of estetrol research, the reasons why one would not have expected estetrol to work, and the unexpected nature of the invention with the Examiner. Other patent applications that recite estetrol and are assigned to the assignee also were discussed. Those applications and their present status are:

U.S. Pat. App. No.	Examiner	Rejections under 35 U.S.C. § 102 or 103
10/478,262	Hui	Rejected under §§ 102 & 103.
10/478,264	Hui	Rejections have been withdrawn. Issue fee paid.
10/478,357	Hui	Rejections have been withdrawn.
10/478,365	Chui	Rejections have been withdrawn.
10/495,707	Sullivan	Rejected under § 103.
10/517,686	Chui	Rejections have been withdrawn.
10/521,040	Chui	Rejections have been withdrawn.

The Section 102 and/or 103 rejections were withdrawn in view of various interviews with Examiner Hui and Chui. On March 30, 2009, Applicants' representative and inventor Herjan Coelingh Bennink conducted an in-person interview with Examiner Hui. Declarant Carolyn Westhoff was present via telephone. During the interview, the history of

[25] Office Action at page 3.

estetrol research and the unexpected results (the long elimination half-life of estetrol, and its pharmacological usefulness) were discussed. At the conclusion of the interview, Examiner Hui requested that the Applicants submit certain evidence that further supports the statements made during the interview. Applicants complied, and consequently, Examiner Hui withdrew the obviousness rejections asserted in U.S. Pat. App. Nos. 10/478,264 and 10/478,357.

The Examiners requested that Applicants submit similar evidence in this matter as well. The following five references were cited in the '264 and '357 Applications, were disclosed in the Information Disclosure Statement dated October 20, 2009, and are discussed below: Visser *et al.* "*In vitro* effects of estetrol on receptor binding, drug targets and human liver cell metabolism," CLIMACTERIC (2008) 11(1) Appx. II: 1-5; Visser *et al.*, "First human exposure to exogenous single-dose oral estetrol in early postmenopausal women," CLIMACTERIC (2008) 11(1): 1-10; Visser *et al.* "Clinical applications of estetrol," J. OF STEROID BIOCHEM AND MOLECULAR BIOL. (2009) 114: 85-89; Holinka *et al.* "Estetrol: A unique steroid in human pregnancy," J. OF STEROID BIOCHEM AND MOLECULAR BIOL. (2009) 110: 138-143; and Coelingh Bennink *et al.*, "Oral bioavailability and bone sparing effects of estetrol in an osteoporosis model," CLIMACTERIC (2008) 11(Supp 3): 1-13.

During the interview with Examiner Hui, Dr. Westhoff stated that each estrogen has a unique profile, and therefore, one would not reasonably expect that one estrogen could be easily substituted for another. This is especially true for estetrol, which is presently considered a selective estrogen receptor modulator ("SERM"). Some relevant differences between estetrol and common estrogens include:

- Estetrol has a 4-5 fold preference of estrogen receptor alpha, whereas ethinyl estradiol and estradiol prefer estrogen receptor beta;[26]

[26] Visser *et al.* "*In vitro* effects of estetrol on receptor binging, drug targets and human liver cell metabolism," CLIMACTERIC (2008) 11(1) Appx. II: 1-5 at page 1, column 2 and page 5, column 1.

- Estetrol has less interaction with liver function, which leads to slower elimination and longer half-life,[27] no active metabolites,[28] no ctyochrome p450 inhibition,[29] no SHBG binding[30] and no desulfation;

- Estetrol acts as an estrogen on the vagina, uterus, bone and brain, but as an estrogen antagonist on breast cells and tumors;[31]

- Estetrol has different ligand/receptor crystallization in docking experiments compared to other estrogens; and

- Estetrol has no subjective side effects up to 40 mg per day for 28 days.[32]

One other significant difference is the bioavailability of estetrol versus estradiol. "Estradiol is partially inactived by binding to SHBG (30%) and loosely bound to albumin (60%), resulting in a biologically free fraction of about 2%."[33] "Ethinylestradiol has a bioavailability of 38-48% due to a marked metabolism in the gut mucosa and during first liver passage ... Ethinylestradiol is bound to albumin and hardly to SHBG, indicating that circulating ethinylestradiol is rather easily bioavailable."[34] In contrast, "E_4 is an end-stage product of metabolism and is not converted into other active metabolites, including estrogens such as estrone (E_1), E_2 or E_3. Second, *in vitro* E_4 does not bind to SHBG and only moderately to albumin. This means that ... the circulating E_4 is readily bioavailable. In this respect, E_4 is comparable to ethinylestradiol,"[35] whereas one would have expected estetrol to be more comparable to estradiol or estriol.

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[27] Visser *et al.*, "First human exposure to exogenous single-dose oral estetrol in early postmenopausal women," CLIMACTERIC (2008) 11(1): 1-10 at page 5, column 1 and page 8, column 2.

[28] Visser *et al.* CLIMACTERIC (2008) Appx. II at page 4, column 1.

[29] Visser *et al.* CLIMACTERIC (2008) Appx. II at page 4, column 2 to page 5, column 1.

[30] Visser *et al.*CLIMACTERIC (2008) at page 9, column 1.

[31] Visser *et al.* CLIMACTERIC (2008) at page 2, column 1.

[32] Visser *et al.* "Clinical applications of estetrol," J. OF STEROID BIOCHEM AND MOLECULAR BIOL. (2009) 114: 85-89 at page 87 and Fig. 4.

[33] Visser *et al.* CLIMACTERIC (2008) at page 9, column 1.

[34] Visser *et al.* CLIMACTERIC (2008) at page 9, column 1.

[35] Visser *et al.* CLIMACTERIC (2008) at page 9, column 1.

Due to these differences, estetrol can be characterized as a SERM.[36] Prior to the disclosure of this invention, SERMs were known as synthetic molecules with different profiles. For example, tamoxifen, an antagonist for breast cell estrogen receptors, is a SERM used for the treatment of breast cancer. Raloxifen is a SERM that has estrogenic activity in bone and anti-estrogenic activity in the uterus and breast. The inventors identified estetrol as the first natural human SERM.[37] In this respect, estetrol is fundamentally different from the other estrogens because, for example, these other estrogens are known to have a stimulatory effect on breast tumors, especially estradiol. Since estetrol does not have a stimulatory effect on breast tumors, it is ideally suited for the recited method.

As Dr. Westhoff mentioned during the interview with Examiner Hui, prior to the disclosure of this invention, there was no reason for one to believe that estetrol would be pharmacologically active at large doses. Nevertheless, even assuming that one believed that some pharmacological activity could be obtained at large doses, he or she would have been concerned of the risk of serious side effects that would be expected to result from delivering large doses of an estrogen. Particularly, since one would have assumed that estetrol behaved like other estrogens, one would have also assumed that it would have a stimulatory effect on breast tumors, and increase the risk of breast cancer. These unwanted side effects would steer one away from considering estetrol as pharmacologically useful at large doses. Therefore, one would not have considered delivering "shovel-loads" of estetrol to a patient. Accordingly, one had no reason to expect estetrol to be pharmacologically useful in the recited method. This point is further demonstrated by the references listed in the specification and discussed in prior responses, and the declarations from third-party artisans in the field.

When making a rejection under 35 U.S.C. § 103, the examiner has the burden of establishing a *prima facie* case of obviousness. *In re Fritch*, 23 U.S.P.Q.2d 1780, 1783 (Fed. Cir. 1992). As part of a *prima facie* case, an examiner must establish some reason to combine the references. *KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 131 (2007); *Takeda Chemical Industries, Ltd. v. Alpharpharm Pty., Ltd.*, 492 F.3d 1350, 1356-1357 (Fed. Cir.

[36] Visser *et al.* CLIMACTERIC (2008) at page 2, column 1.

[37] Visser *et al.* CLIMACTERIC (2008) at page 2, column 1.

2007). The *KSR* Court acknowledged the importance of identifying a reason that would have prompted a person of ordinary skill in the art to combine the elements in the way the claimed invention does. *KSR Int'l*, 127 S.Ct. at 1731; *Takeda Chemical*, 492 F.3d at 1356-1357. Repeatedly throughout the *KSR* decision, the Court discussed the importance that the result obtained by a particular combination was predictable to one of ordinary skill in the art. *KSR Int'l*, 127 S.Ct. at 1731 and 1739-1742.

A combination of known elements will not yield predictable results if the references teach away from the claimed invention. *Takeda Chemical*, 492 F.3d at 1359; *Ortho-McNeil Pharmaceutical, Inc. v. Mylan*, 520 F.3d 1358, 1364 (Fed. Cir. 2008); and *Ex parte Ikeda*, App. No. 08/352,079, Appeal 2008-0492, Slip Op. at 7 (BPAI Mar. 26, 2008). For example, in *Takeda Chemical*, the post-*KSR* Federal Circuit noted that the recited compound, which was a modified version of compound b, was not recognized at the pertinent time as a suitable candidate for treatment of Type II diabetes. 492 F.3d at 1359. *Takeda Chemical* involved United States Patent No. 4,687,777, which was directed to a compound for the treatment of Type II diabetes. *Id.* at 1352-1354. The defendant argued that the patent was obvious in view of a reference that disclosed compound b, because the claimed compound could be synthesized from compound b by routine means. *Id.* at 1357. However, the Federal Circuit affirmed that the patent was not obvious because the prior art taught away from choosing compound b as a starting point. *Id.* at 1359-1361. Compound b was known to have unwanted side effects, and there was nothing in the prior art to suggest that homologation would decrease the unwanted side effects. *Id.* at 1359-1360.

In a more recent case, the Board reversed an examiner's rejection for failing to provide the requisite reason to combine the references. *Ikeda*, App No. 08/352,079 at 7. The *Ikeda* application was directed to a method of removing hydrocarbons from exhaust gases. *Id.* at 2. In pertinent part, the claims recited an absorption catalyst B located downstream of a catalyst A in the direction of the exhaust gas. The claims were rejected as unpatentable under 35 U.S.C. § 103 in view of Swaroop, Abe and Patil. *Id.* at 3. Swaroop taught positioning the absorption catalyst B upstream of catalyst A. *Id.* at 5. To remedy the deficiency in the art, the examiner cited "Patil and Abe as evidence of the 'conventionality of positioning the adsorbent catalyst 1 either upstream or downstream of a [three-way] catalyst 3' and thus conclude[d] that it would have been obvious to one of ordinary skill in this art to select an

appropriate location for the adsorbent catalyst 16 in the apparatus of Swaroop ...." *Id.* at 5-6.

The Board held that

> The Examiner has failed to provide any cogent reason or technical discussion to support the conclusion that one of ordinary skill in this art would have employed the relative positions of the catalysts in Abe and Patil without the use of the other teachings of these references, namely an auxiliary heater and bypass lines with valving. Second, the Examiner has not explained why one of ordinary skill in this art would have used the teachings of Patil, requiring bypass lines and valving, when Swaroop specifically ***teaches away*** from the use of valving and bypass lines [*citation omitted*]. Third, the Examiner has not supplied convincing reasoning or technical discussion to support the proposed switch in relative position of the catalysts when Swaroop specifically teaches that the exhaust gas is "modified" by the adsorbent catalyst and this modified form of the exhaust gas is *then* sent to the main or three-way catalyst to undergo conversion to innocuous products [*citation omitted*]. ... Fourth, the Examiner has not explained why one of ordinary skill in this art would have ***proceeded contrary to the teachings of Patil***, namely the teachings that "it is not possible merely to place zeolite 'in-line' in the exhaust system with the [main] catalyst has reached an effective temperature and unconverted hydrocarbons would still be discharged to the atmosphere" [*citation omitted*].

Emphasis added, *Ikeda*, App. No. 08/352,079 at 7.

Following the reasoning stated in *Takeda Chemical* and *Ikeda*, the Office Action must provide some explanation why one of ordinary skill in the art would believe that estetrol would be pharmacologically useful when estetrol was believed to have too little estrogenic potency to be useful. As discussed above, prior to the publication of this invention, one of ordinary skill in the art would not expect estetrol to be pharmacologically useful because it was known that estetrol was a considerably weaker estrogen than the already weak estrogen estriol.

It was not until the Applicants discovered estetrol's very long terminal elimination half-life that it became apparent that estetrol could be pharmacologically useful. Prior to the disclosure of this invention, there was no publicly available data about the terminal elimination half-life of estetrol, about estetrol's binding to SHBG or about estetrol's effect on SHBG production.[38] Since estradiol and estriol have terminal elimination half-lifes of about 30 minutes and 5-10 minutes, respectively, it was believed that estetrol, another

[38] Declaration by Coelingh Bennink at ¶¶ 4.

natural estrogen, would likewise have a short, if not shorter, terminal elimination half-life.[39] Unexpectedly, the Applicants discovered that estetrol has a terminal elimination half-life of about 28 hours.[40]

> A person of ordinary skill in the art would have expected estetrol to be more comparable to estriol than estradiol given that (i) estetrol differs from estriol by only 1 hydroxy group and from estradiol by 2 hydroxy groups and (ii) both estriol and estetrol are produced during pregnancy. Hence, Applicants' finding that estetrol has a terminal elimination half-life that is 168-336 higher than that of the other pregnancy hormone estriol, was very unexpected and provided the clue towards its pharmacological usefulness.[41]

Like *Takeda Chemical*, one of ordinary skill in the art would have had no reason to use estetrol because it was believed not to be pharmacologically useful. Maintaining a rejection based on the premise that estetrol can be used instead of estrone (E_1), estradiol (E_2) or estriol (E_3) is improper for the same reasons that the rejection in *Ikeda* was improper – because the prior art teaches away from using estetrol. As part of a *prima facie* case of obviousness, there must be some explanation why one of ordinary skill in the art would consider using estetrol when the prior art teaches that it is not pharmacologically useful. Since such an explanation has not been provided, a *prima facie* case of obviousness has not been established.

In order for the invention to be obvious, there must have been a reason to select estetrol over the other estrogen compounds. However, one would not have had a reasonable expectation that estetrol would be pharmacologically useful prior to the disclosure of this invention. Nor would one have reasonably expected that estetrol could be used successfully in the method taught by Kragie.

Prior to the disclosure of this invention, a person of ordinary skill would have been surprised to learn that estetrol was pharmacologically useful because, as previously established, estetrol had a very low receptor affinity,[42] and was expected to have a very short

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[39] Declaration by Strauss at ¶ 18; Declaration by Speroff at ¶ 18; and Declaration by Westhoff at ¶18.

[40] Declaration by Strauss at ¶ 18; Declaration by Speroff at ¶ 18; and Declaration by Westhoff at ¶18.

[41] Declaration by Strauss at ¶ 18; Declaration by Speroff at ¶ 18; and Declaration by Westhoff at ¶18.

[42] Declaration by Strauss at ¶¶ 15-16; Declaration by Speroff at ¶¶ 15-16; Holinka (1979); and Holinka (1980).

half-life.[43] Consequently, despite the fact that Kragie mentions estetrol as an example of an EFR agent, one of ordinary skill in the art would not have reasonably expected that he or she could successfully use estetrol in the method taught by Kragie since, in view on all the pharmacological data about estetrol that was available at the time, it was believed that estetrol was too weak and had a too short of a half-life to be pharmacologically useful.

Point II. It was unexpected to discover that estetrol was pharmacologically useful.

The Applicants also maintain that the unexpected results – estetrol's potency and long elimination half-life – provide an additional reason why the recited invention is patentable over the cited references. During the interview with Examiner Hui, Dr. Coelingh Bennink and the Examiner discussed the significance of the elimination half-life. In summary, Dr. Coelingh Bennink stated that pharmakinetics and pharmadynamics are interconnected with regard to potency. The Examiner requested that we provide some additional support for these statements.

A compound's ADME (absorption, distribution, metabolism and excretion) properties and non-receptor mediated non-genomic effects are important predictive factors of the theoretical potency of a steroid or drug that interacts with a steroid receptor. The elimination half-life is an important aspect of ADME properties. All other things being equal, the longer a drug is circulating in the blood, the stronger its potency will be. This happens to be the case with estetrol. As previously established, prior to the disclosure of this invention, it was believed that estetrol had low receptor binding and a short elimination half-life. The affinity of estetrol is about 5% compared to estradiol.[44] Furthermore, the chemical similarities between estetrol and estriol lead one to expect that estetrol has a similar or shorter elimination half-life than estriol (20 minutes).[45]

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[43] Declaration by Strauss at ¶ 18; Declaration by Speroff at ¶ 18; and Declaration by Westhoff at ¶18.

[44] Holinka *et al.* "Estetrol: A unique steroid in human pregnancy," J. OF STEROID BIOCHEM. AND MOLECULAR BIOL. (2009) 110: 138-143 at page 142, column 1, citing Martucci *et al.*, "Uterine estrogen receptor binding of catecholestrogens and of estetrol (1,3,4(10-estraiene-3, 15a, 16a 17b-tetrol)," STEROIDS (1976) 27: 325-333.

[45] Declaration by Westhoff at ¶ 16; Visser *et al.* CLIMACTERIC (2008) at page 2, column 2.

Based on the low affinity and expected short half-life, one would have expected estetrol's estrogenic potency to be much lower than estradiol's. Holinka teaches that estriol is 50 times more potent than estetrol.[46] Estriol is a natural estrogen that has a weaker potency than estradiol.

Holinka further states that "[e]stetrol produced small statistically significant increases in uterine weight to 55% above the pretreatment levels compared to 300% after E_2 treatment at a 50x lower dose of E2."[47] Thus, at a fifty-times-greater dose, estetrol increased the uterine weight only approximately $1/6^{th}$ that of estradiol. Consequently, one would have expected estradiol to be at least 300 times ($50 \cdot 6$) more potent than estetrol; however, estetrol is in fact as potent, or, at worst, slightly weaker than estradiol.

This is very unexpected. Although not wishing to be bound by theory, Dr. Coelingh Bennink stated that this unexpected potency is due to estetrol's long elimination half-life because estetrol circulates in the blood for approximately 168-336 times longer than estriol and 56 times longer than estradiol.[48]

This unexpected long half-life allows estetrol to circulate in the blood much longer than its most closely related estrogen, estriol. Consequently, even though estetrol is expected to be more than 300 times weaker than estradiol, due to the prolonged presence of estetrol in the blood, it has a greater than expected potency. This unexpected potency reaches a level that makes estetrol pharmacologically useful. Furthermore, since estetrol is a breast tumor antagonist, it does not have the health risks that are associated with other estrogens, such as estradiol and ethinyl estradiol.

Therefore, estetrol's unexpected long elimination half-life is directly related to the unexpected pharmacological uses of estetrol. For these additional reasons, Applicants respectfully submit that the recited invention is patentable over the cited references.

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[46] Declaration by Westhoff at ¶¶ 15-16; Holinka (1979); and Holinka (1980). These studies were done *in vitro*, and therefore, the half-life of estetrol was not measured.

[47] Holinka *et al.*, J. OF STEROID BIOCHEM. AND MOLECULAR BIOL. (2008) at page 141, column 1.

[48] Declaration by Westhoff at ¶ 18.

The unexpected result that estetrol is pharmacologically useful because it has a long terminal elimination half-life rebuts the obviousness rejection. See *Ormco Corp. v. Align Technology, Inc.*, 463 F.3d 1299, 1311, (Fed. Cir. 2006); see also *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995). To establish unexpected results, the Applicant must "establish (1) that there actually is a difference between the results obtained through the claimed invention and those of the prior art, *In re Klosak*, 455 F.2d 1077, 59 CCPA 862 (1972); and (2) that the difference actually obtained would not have been expected by one skilled in the art at the time of invention, *Id.*; *In re D'Ancicco*, 439 F.2d 1244, 58 CCPA 1057 (1971)." *In re Freeman*, 474 F.2d 1318, 1324 (CCPA 1973). Without evidence to the contrary, an applicant need only provide substantially improved results and state that the results were unexpected. *Soni*, 54 F.3d at 750; *In re Lee*, App No. 10/091,061, 2007 WL 176690 at *3 (BPAI June 19, 2007).

In *Soni*, the examiner rejected certain claims as obvious in view of a combination of references. The applicant directed the examiner to the data in the specification, and argued that the increase in tensile strength and the increase in peel strength rebutted the rejections. *Soni*, 54 F.3d at 747. On appeal to the Federal Circuit, it was argued that the Board "could have taken judicial notice of the fact that higher molecular weight polymers would have been expected to tolerate higher filler loadings without degradation in properties and that it could have taken notice of the fact that it is the polymer *per se* that primarily determines the mechanical properties of a filled polymer composition." *Id.* at 750. However, the Federal Circuit found this argument fatally flawed because the Board failed to support its position with facts or evidence. *Id.* at 750; see also *Lee*, 2007 WL 176690 at *3. In summary, the Federal Circuit held that "[m]ere improvement in properties does not always suffice to show unexpected results. In our view, however, when an applicant demonstrates *substantially* improved results, as Soni did here, and *states* that the results were *unexpected,* this should suffice to establish unexpected results *in the absence of* evidence to the contrary." *Soni*, 54 F.3d at 751.

Estetrol has a terminal elimination half-life of 28 hours, which is 168-336 times greater than estriol's terminal half-life and about 56 times greater than estradiol's terminal half-life.[49] Thus, there is an actual difference and substantial improvement between estetrol and estriol as well as between estetrol and estradiol.

One of ordinary skill in the art would have expected estetrol to be more comparable to estriol than estradiol given that (i) estetrol differs from estriol by only one hydroxyl group and from estradiol by two hydroxyl groups and (ii) both estriol and estetrol are produced during pregnancy.[50] Thus, one of ordinary skill in the art would have expected estetrol to have a terminal elimination half-life similar to estriol – on the order of a few minutes.[51] Unexpectedly, the Applicants discovered that estetrol's terminal elimination half-life was 28 hours.

The unexpectedly long terminal elimination half-life is associated with the unexpected pharmacological activity of estetrol. As discussed above, estetrol was known to be a very weak estrogen, so much so that it was dismissed by those of ordinary skill in the art as not being pharmacologically useful.[52] Thus, it was unexpected to discover that estetrol, due to its unexpectedly long terminal elimination half-life, would be pharmacologically useful.

Therefore, even assuming that a *prima facie* case of obviousness has been established, the unexpected results – that estetrol has an unexpectedly long terminal elimination half-life, and/or that estetrol is pharmacologically useful – provide evidence that the recited invention is patentable over the cited references.

[49] Declaration by Strauss at ¶ 18; Declaration by Speroff at ¶ 18; and Declaration by Westhoff at ¶18.

[50] Declaration by Strauss at ¶ 18; Declaration by Speroff at ¶ 18; and Declaration by Westhoff at ¶18.

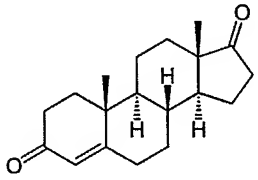
[51] Declaration by Strauss at ¶ 18; Declaration by Speroff at ¶ 18; and Declaration by Westhoff at ¶18.

[52] Declaration by Coelingh Bennink at Exhibit B.

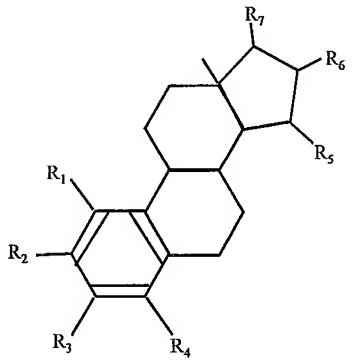
Point III. Younglai does not teach the recited precursor.

Claim 28 has been rejected as unpatentable over Kragie, Willhite and Younglai;[53] or Sitruk-Ware, Spicer, Willhite and Younglai.[54] In these rejections, the Patent Office contends that Younglai teaches many precursors of estetrol, for example 15-α-hydroxyandrostenedione.[55]

Androstenedione is represented by the following chemical structure:



Claim 28, as amended, requires that the precursors are derivatives of the estrogenic substances represented by the following formula:



in which formula R_1, R_2, R_3, R_4, independently are a hydrogen atom, a hydroxyl group or an alkoxy group with 1-5 carbon atoms; each of R_5, R_6, R_7 is a hydroxyl group; no more than 3 of R_1, R_2, R_3, R_4 are hydrogen atoms;

precursors capable of liberating a substance according to the aforementioned formula when used in the present method, wherein the precursors are derivatives of the estrogenic substances wherein the hydrogen atom of at least one of the hydroxyl groups has been substituted by an acyl radical of a hydrocarbon carboxylic, sulfonic acid or sulfamic acid of 1-25 carbon atoms;

[53] Office Action at pages 11-12.

[54] Office Action at pages 15-16.

[55] Office Action at page 12.

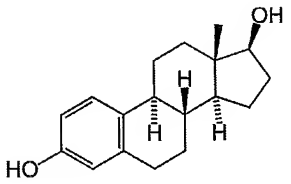
tetrahydrofuranyl; tetrahydropyranal; or a straight or branched chain glycosydic residue containing 1-20 glycosidic units per residue; and

mixtures of one or more of the aforementioned substances and/or precursors; and

(ii) a cosmetically acceptable vehicle.

Claim 28 *de facto* requires (i) that the ring carrying substituents R_1, R_2, R_3, R_4 comprises three unsaturated bonds and (ii) that R_6 and R_7 each independently represent a hydroxyl group or an O-acyl, wherein acyl is an acyl radical as defined above. Since neither dehydroandrostenedione nor 15-α-hydroxyandrostenedione meet these requirements, the combined teachings of Kragie, Willhite, and Younglai could not have led a person of ordinary skill in the art to the subject matter of present claim 20.

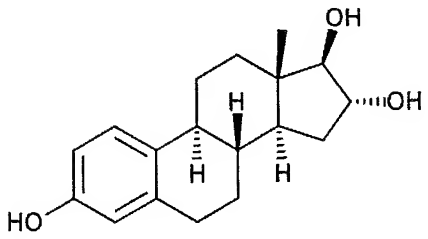
On page 4, the Examiner contends that "the claims do not require R_1, R_2, R_3, and R_4 to be OH or addition of three unsaturated bonds."[56] However, during the interview of December 2, 2009, the Examiners abandoned this argument and instead argued that Younglai Fig. 2 teaches that E_2 and E_3 are precursors of E_4. Neither E_2 nor E_3 are encompassed by claim 28, as amended. Estradiol (E_2) has the following chemical structure:



With regard to precursors, claim 28 recites "wherein the hydrogen atom of at least one of the hydroxyl groups has been substituted by an acyl radical of a hydrocarbon carboxylic, sulfonic acid or sulfamic acid of 1-25 carbon atoms; tetrahydrofuranyl; tetrahydropyranal; or a straight or branched chain glycosydic residue containing 1-20 glycosidic units per residue." Estradiol is not a precursor as recited in claim 28 because E_2 does not have at least one of the hydroxyl groups substituted with an acyl radical of a hydrocarbon carboxylic, sulfonix acid or sulfamic acid; a tetrahydrofuranyl; a tetrahydropyranal; or a glycosydic residue.

[56] Office Action at page 4.

Likewise, estriol (E_3) likewise does not have such a substitution on at least one of the hydroxyl groups. Estriol has the following chemical structure:



Estriol is not a precursor to estetrol as defined by claim 28 for the same reasons that E_2 is not a precursor.

CONCLUSION

Accordingly, Applicants respectfully request that the asserted rejections be reconsidered and withdrawn, and that claims 18-19, 24, 26, 28 and 32-34 be allowed.

Respectfully submitted,

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